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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/082,112	05/20/1998	ALBERTO L. MENDOZA	MSU4.1-406	2322

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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/082,112	Mendoza
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 12-27-01

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 16-25 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 16-25 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. The amendment filed 12-27-01 has been entered into the record and has been fully considered.

2. Claims 16-25 are pending.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 19 and 24 stand rejected as set forth in Paper No. 32 mailed 8-13-01 as indefinite for the recitation of "removing the disrupted cells to provide the mixed intracellular proteins". Such recitation is indefinite to the skilled artisan as to what is being removed or what steps are being performed. Applicant's are suggested to recite a step which may be discerned by the artisan such as removing insoluble material by centrifugation.

Applicants argue that the claims have been amended to overcome the rejection.

Applicants arguments have been fully considered but are not persuasive. For example the specification in Example 1 sets forth steps for the preparation of the vaccine yet claims the vaccine in different method terms. As extensively argued in the previous rejections of record, the artisan fails to recognize immediately separable intracellular and extracellular material. Applicants appear to be referring to the removal of insoluble cellular material via centrifugation and removal of the supernatant with discarding of the pellet. Yet the artisan does not readily recognize how removal of disrupted cells may be achieved and therefore the recited step is

indefinite as to what step is being performed and its effect on the vaccine prepared by the recited method. Clarification is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 16-25 stand rejected under 35 U.S.C. 103(a) as set forth in Paper Nos. 23, 26, 32 and as set forth herein as being unpatentable over Mendoza et al, J. Mycol. Med, 1996, 6:151-164, Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI), Mendoza et al, J. Clin. Microbiology, Nov. 1992(b), p. 2980-83, Sigma Catalog, p.1874, 1992, Amicon Catalog, p. 35, 1993 and Mendoza et al., Abstract, Third NIAID Workshop in Medical Mycology Series, September 7-9, 1995.

Applicants traverse the 103 rejection in pp. 8-11 of the response filed 12-27-01. At the paragraph spanning p. 8-9, applicants argue that the artisan would not expect the combined vaccine (CMV and SCAV) to provide the result of the claimed vaccine as neither the CMV nor SCAV alone was able to cure chronically infected horses.

In response, the examiner notes that applicant's fail to acknowledge that the suggestion of the combination and the effect of curing chronically infected horses are provided in the prior art. Specifically, the prominent cytoplasmic (intracellular) antigens were added as described in

Mendoza et al., J. Clin. Microbiol., 30:2980-2983, 1992(b) to the SCAV vaccine (mixed extracellular preparation). Mendoza et al., Abstract 1995, teaches that the addition of the 28-32 kD immunodominant (intracellular) peptides to the culture filtrate proteins leads to the cure of 8 chronically infected horses. As discussed in the Mendoza et al., 1992(b) reference, Mendoza thus teaches that the addition of intracellular cytoplasmic antigens provides for the improved vaccine which cures chronically infected horses. In detail and as set forth in the specification at page 6, line 15, the improved vaccine (was) prepared by adding cytoplasmic antigens to the earlier *P. insidiosum*-vaccine (Mendoza et al., Mycopathologica 119:89-95 (1992(a))). Mendoza et al, 1992(a) disclose two prior art vaccines, a cell-mass vaccine (CMV) and a soluble concentrated antigen vaccine (SACV). Mendoza et al., Abstract 1995, teaches that the addition of the 28-32 kD (intracellular) immunodominant peptides to culture filtrate proteins leads to the cure of 8 chronically infected horses. As discussed, the Mendoza et al., 1992(b), reference thus suggests and teaches the combination of mixed intracellular and mixed extracellular antigens as claimed and thus provides the motivation for the improved vaccine in addition to its' expected benefits, curing chronically infected horses. The methodology disclosed for the preparation of the two vaccines and the isolation of the three added immunodominant peptides are referenced at p. 2981, column 1 as disclosed in Mendoza et al., J. Clin. Microbiol., 30:2980-83, 1992. Mendoza in this publication clearly evidences that the three immunodominant proteins which are added to the improved vaccine are present in the CMV preparation, represent immunodominant peptides and further suggests that such peptides may be useful for diagnostic and immunotherapeutic

effects in horses, see in particular abstract and 2981, column 1, including for treatment of chronically infected horses, see in particular Mendoza et al., 1995 and 1996.

At the paragraph spanning p. 9-10 applicants argue that the prior art provides no motivation to combine *all* (not just the immunodominant 28-32 kD intracellular proteins) of the extractable intracellular proteins with the vaccine comprising extracellular proteins and that the prior art suggests that the vaccine consisting of all the intracellular proteins added to the SCAV vaccine would not produce the same result because the CMV vaccine was unable to cure chronically infected horses. Applicants interpret this as a teaching that the CMV preparation contained other constituents which interfered with the ability of the three immunodominant proteins to cure horses. Applicants argue that the teachings only suggest a combination of the extracellular preparation with the addition of the three immunodominant proteins, but not all of the intracellular proteins of the CMV vaccine.

In response, the fact that the CMV vaccine alone was not able to cure chronically infected horses is not a teaching that the CMV preparation contained components which inhibited the curative properties of the immunodominant proteins as the comparative data provided is insufficient to arrive at such conclusion. In contrast, the prior art does not teach that the immunodominant proteins are the critical element. The prior art teaches that a combination of the SCAV (extracellular) preparation with the addition of the immunodominant proteins (contained in the CMV preparation) was the critical combination. Thus, the suggestion of the prior art is alternatively that the combination of mixed intracellular and extracellular proteins

provide the enhanced curative properties to chronically infected horses. In addition, upon such teaching, the combination of the CMV (containing the immunodominant proteins) and the SCAV (mixed extracellular) proteins would have been prima facie obvious to the artisan, particularly in that the combination of the two preparations would provided the required constituents yet would be easier in preparation than providing only the isolated immunodominant proteins as there would be no need for the additional preparative steps including isolation of the 28-32 kD antigens via gel electrophoresis, recovery from the gel and addition to the SCAV vaccine. Thus, in contrast to applicant's suggestion, the prior art suggests the mixture of intracellular and extracellular proteins and the artisan would recognize that the easiest way of performing such combination would be to combine the intracellular (CMV) and extracellular (SCAV) preparations of the prior art which have been shown to contain the minimal essential elements required for curing chronically infected horses. It is noted that as the claims recite comprising language, the elements of the claimed invention i.e., mixed intracellular and mixed extracellular proteins are provided and are within the scope of the claim regardless of whether all of the intracellular antigens or merely the immunodominant intracellular antigens are provided. *All* of the intracellular proteins are not required by the claims. The steps provided in the claims are those for the preparation of the CMV and SCAV vaccines. It is further noted that there is no comparative data which demonstrates different or unexpected effects which are attributed to a preparation containing all the intracellular proteins in comparison to one containing only the immunodominant peptides.

In the second paragraph of p. 10, applicants argue that the Sigma Catalogue provides no teaching to render the invention obvious with respect to a preparation consisting of all the extractable intracellular proteins with the extracellular proteins when viewed with the prior art.

In response, it is noted that applicants claims are not directed to a preparation "consisting of all the extractable intracellular proteins with the extracellular proteins" as argued. In addition, it is noted that the Sigma reference is directed to the equivalent step of removing low molecular weight constituents via a PM-10 membrane as disclosed for example in Mendoza et al., J. Clin. Microbiol., Nov. 1992, p. 2980-83 as set forth in p. 8-9 of the office action mailed 11-7-00 and the limitation as recited in the method of claims 16-25 of "dialyzing the resuspended proteins in sterile water to remove material less than 10,000 MW". The method/process limitations of filtration via ultracentrifugation or a stir cell through a PM-10 membrane remove small peptides and impurities as set forth previously and in particular is evidenced by Table 19 of the provided Amicon catalog p. 35. This step is an obvious equivalent which does not appear to result in a patentably distinguishable product from that of dialysis to remove small peptides and impurities because the molecular weight cut offs for the PM-10 membrane and a dialysis membrane are similar as evidenced by Sigma, Amicon and Mendoza et al., 1992(b) as set forth at p. 8-9 of the office action of 11-7-00, Paper No. 26 and as set forth herein. The previous office action sites Sigma for dialysis tubing with a molecular weight cutoff of approximately 12,400 MW and PM-10 membrane of MW cut-off of 10,000 MW. The examiner provides herein the MW of Thimerosal as evidenced by Sigma, p. 952 of 404.8 MW and thus it is clear that Thimerosal

would be removed by either dialysis or ultracentrifugation through a PM-10 membrane. Thus, the Sigma reference is relevant to the claimed method step.

At the paragraph spanning pp. 10-11 applicants argue that the examiner is using hindsight reconstruction to reject applicant's claims.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the second paragraph of p. 11 applicants argue that the prior art fails to suggest the use of the claimed vaccine in humans and that because humans and horses are not evolutionarily related, it is unlikely that one of ordinary skill of the art would have considered a veterinary vaccine for use in humans.

In response, without arguing the evolutionary descent of horses and humans, suffice it to say that the artisan at least recognizes horses and humans as common mammals which exhibit strikingly similar immune response mechanisms as previously set forth in Paper No. 23, 1107-00, pp. 10-11 including T cells, B cells, antibodies, cytokines etc.. Thus, there is no apparent reason why the artisan would a priori determine that an efficacious vaccine in horses would necessarily

fail to be beneficial to humans. Yet still, the previous rejection provides further evidence which suggests that the artisan would expect that the combined prior art vaccine would possess similar protective responses in horses and humans. In particular Mendoza et al., 1996 clearly indicate the similarity in human and animal Pythiosis infections, the need for treatment in humans as noted above that the same immunodominant antigens were recognized in horse and human sera and that these immunodominant antigens correspond to the 28-32 kD immunodominant antigens contained in the CMV intracellular preparation and which have been shown to provide the enhanced curative properties in chronically infected horses when combined with the SCAV extracellular vaccine of the prior art. Thus, based on Mendoza et al., 1996 the artisan would have motivation to provide the combined vaccine to humans and would further expect beneficial results based on the evidence that the critical immunodominant epitopes required for protection in horses and humans are the same. Thus based on the cumulative reference teachings the claimed invention is rendered prima facie obvious to the skilled artisan. There are no method steps as claimed which are not provided by the prior art and the motivation and expectation of success for the combination are provided by the reference teachings.

Consistent with case law and as set forth in the MPEP 2144.06, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)."

Status of Claims

7. No claims are allowed.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
February 5, 2002

Gary L. Kunz
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